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December 23, 2003

Michael O. Leavitt, Administrator
U.S. Environmental Protection Agency
Ariel Rios Building (1101A)
1200 Pennsylvania Ave., NW
Washington, DC 20460

Re: Comments on the HPV test plan for Thiodiethylene bis (3,5-di-tert-butyl-4-hydroxyhydrocinnamate)

Dear Administrator Leavitt:

The following are comments on the HPV test plan for Thiodiethylene bis (3,5-di-tert-butyl-4-hydroxyhydrocinnamate) (IRGANOX 1035) (CAS no. 41484-35-9), submitted by Ciba Specialty Chemicals Corporation (Ciba). These comments are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These animal, health and environmental protection organizations have a combined membership of more than ten million Americans.

Ciba submitted its test plan on August 8, 2003 for IRGANOX 1035. The Council proposes to do an OECD 414 Test Protocol, a developmental test, which will kill approximately 1300 animals. While there is no available reproductive endpoint, Ciba proposes to use data gained from the proposed developmental test, in conjunction with available reproductive organ data from prior subchronic studies, to satisfy this endpoint. While this approach might seem creative and meet the intent of the HPV program, there is in fact a more effective way to do this and to greatly reduce the number of animals killed (see below).

The major uses and human exposure scenarios are briefly described in the test plan, along with general substance information. Major human exposure occurs only in the workplace, with consumer exposure being extraordinarily low. In addition, this chemical has already been cleared by the FDA as an indirect food additive for use "in polymers, resins or adhesives intended for food contact applications" (test plan, p. 2). IRGANOX 1035 appears to be non-toxic through multiple routes (oral, dermal, and inhalation), with an oral LD50 value of greater than 5 g/kg in the rat, and an acute dermal LD50 value of greater than 3 g/kg in the rabbit, and an acute inhalation LD50 of over 6.3 g/m^3 in the rat. Moreover, subchronic data give further evidence to its non-toxic characteristics, as NOELs have been calculated ranging from 60 to 10,000 ppm in rats and dogs. These subchronic studies included a histological examination of all internal organs and showed no significant toxic effects.

In considering all available exposure and toxicity data available, Ciba is using "check-the-box toxicology" in proposing to conduct more animal studies with this non-mutagenic, non-toxic chemical which is already approved as an indirect food additive by the FDA. The fact is that additional animal testing on a substance of this nature violates principles set forth in both the October 14, 1999, letter to HPV participants and the December 2000 *Federal Register* notice (Wayland, S.H., Oct. 4, *http://www.epa.gov/chemrtk/ceoltr2.htm*; *Federal Register*, "Data collection and development on HPV chemicals," Vol. 65, No. 248, Dec. 26, p. 81691) which specifically state that:

> *In analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there is sufficient data, given the totality of what is known about a chemical, including human experience, that certain endpoints need not be tested.*
>
> *As with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be useful or relevant.*

If Ciba insists on conducting a toxicological test for the developmental endpoint, we strongly urge the use of OECD Test Protocol 421, the reproductive/developmental screen, which would save approximately 675 animals while addressing both SIDS endpoints. The OECD 414 is not warranted, especially since EPA recommended in the Federal Register Notice (FR/Vol. 65, No. 248, Tuesday December 28, 2000) the combined protocol be used. Furthermore, EPA does not reference the use of OECD 414 in the FR for the developmental endpoint. Ciba should follow the EPA recommendation and use the combined protocol using fewer animals.

We also request that Ciba conduct the rodent embryonic stem cell test (EST) in parallel to the combined screen. As you are aware, this *in vitro* embryotoxicity test method has been validated by the European Centre for the Validation of Alternative Methods, and the Centre's Scientific Advisory Committee has concluded that this test is ready to be considered for regulatory purposes (Genschow 2002). The animal protection community has urged individual companies to consider the use of this test, and has provided validation and SOP references. We suggest that, in this screening level program, a positive result found in the EST should warrant the substance's treatment as a developmental toxicant/teratogen, and that no further testing should then be carried out.

Several individual companies have expressed interest in running the EST in parallel with the OECD 421. Though doing so will not spare any animals' lives in the current context, it does help build a database for industrial chemicals for eventual validation of the EST in the U.S. To its credit, at least one company has agreed to the extra expenditure of funds to run four of its HPV chemicals through the EST. It is also worthy of note that the cost of the test is a fraction of the cost of the 421. We would be happy to provide further information on a local laboratory that conducts this test.

We hope to receive a positive response to these comments. Thank you for your attention. I may be reached at 202-686-2210, ext. 335, or via e-mail at *kstoick@pcrm.org*.

Sincerely,

Kristie M Stoick, M.P.H.
Research Analyst

Chad B. Sandusky, Ph.D.
Director of Research